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(54) Title: BISPHOSPHONATE THERAPY FOR BONE LOSS ASSOCIATED WITH RHEUMATOID ARTHRITIS

(57) Abstract

Bisphosphonates, and particularly alendronate, can prevent or treat bone loss associated with rheumatoid arthritis.

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TITLE OF THE INVENTION

BISPHOSPHONATE THERAPY FOR BONE LOSS ASSOCIATED WITH RHEUMATOID ARTHRITIS

SUMMARY OF THE INVENTION

This invention relates to the use of bisphosphonates, particularly alendronate, to prevent bone loss associated with rheumatoid arthritis.

BACKGROUND OF THE INVENTION

Rheumatoid arthritis (RA) is a chronic, multisystemic disease of unknown cause. The characteristic feature of RA is persistent inflammatory synovitis, usually involving peripheral joints. One hallmark of the disease is cartilage destruction and periarticular bone erosion caused by synovial inflammation, resulting in joint deformities. The cell believed to be responsible for the erosive process in the osteoclast. In patients with RA, therapy often includes glucocorticoid administration, immobilization of joints, cyclosporine or methotrexate, all of which may potentiate bone loss and deformity.

It would be desirable to prevent or treat generalized and periarticular bone loss associated with RA.

DETAILED DESCRIPTION OF THE INVENTION

It has been found in accordance with this invention that bisphosphonates can prevent and treat bone loss associtated with rheumatoid arthritis when administered in either a prophylactically or therapeutically effective amount.

In particular, alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonate) or a pharmaceutically effective salt thereof, can prevent and treat bone loss associated with rheumatoid arthritis when administered either in a prophylactically or therapeutically effective amount.

A further aspect of this invention is a method of preventing or treating generalized and/or periarticular bone loss associated with

rheumatoid arthritis comprising administering an effective amount of a bisphosphonate selected from the group consisting of: alendronate, etidronate (1-hydroxy-ethidene-bisphosphonic acid), pamidronate (3-amino-1-hydroxypropyildiene-1,1-diphosphanate), risedronate (2-(3-pyridinyl)-1-hydroxyethylidene-bisphosphonic acid), clodronate (dichloromethylene-bisphosphonic acid), tiludronate (chloro-4-phenylthio-methylidene-bisphosphonic acid), ibandronic acid (1-hydroxy-3(methylpenty-lamino)-propylidene-bisphosphonic acid, and pharmaceutically acceptible salts of any of the foregoing, and mixtures of any of the acids and any of the salts to a patient suffering from rheumatoid arthritis. All of the foregoing compounds are well known in the art.

Generally the patient undergoing treatment for rheumatoid arthritis will be receiving one or more of: an immunosuppressive drug, cyclosporine, methotrexate, or glucocorticoids.

As used throughout the specification and claims, the following definitions apply:

"Prophylactically effective amount"--the amount of alendronate needed to prevent or lessen the severity of bone loss associated with rheumatoid arthritis.

"Therapeutically effective amount"--the amount of alendronate needed to treat bone loss associated with rheumatoid arthritis.

In a preferred aspect of this invention, the patient will receive alendronate. Alendronate may be prepared according to any of the processes described in U.S. Patents 5,019,651, 4,992,007, and U.S. Application Serial No. 08/286,151, filed August 4, 1994, each of which is hereby incorporated by reference. The pharmaceutically acceptable salts of alendronate include salts of alkali metals (e.g., Na, K), alkaline earth metals (e.g. Ca), salts of inorganic acids, such as HCl and salts of organic acids such as citric acid and amino acids. Sodium salt forms are preferred, particularly the monosodium salt trihydrate form.

Many of the bisphosphonate compounds of the present invention can be administered in oral dosage forms such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, paste, tinctures, suspensions, syrups, emulsions, and zydis. Likewise they may be administered in an intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the bisphosphonate compound desired can be used as a an agent which treats or prevents bone loss associated with RA.

The dosage regime utilizing the claimed method is selected in accordance with a variety of factors including type, age, weight, sex, and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or clinician can readily determine and prescribe the effective amount of the drug required to prevent and or treat bone loss.

Oral dosages of the present invention when alendronate is the bisphosphonate will range from between 0.05 mg per kg of body weight per day (mg/kg/day) to about 1.0 mg/kg/day. Preferred oral dosages in humans may range from daily total dosages of about 2.5-50 mg/day over the effective treatment period, and a preferred amount is 5, 10 or 20 mg/day.

Alendronate may be administered in a single daily dose or in a divided dose. It is desirable for the dosage to be given in the absence of food, preferably from about 30 minutes to 2 hours prior to a meal, such as breakfast to permit adequate absorption.

In the methods of the present invention, the active ingredient is typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier materials") suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules, elixirs, syrups and the like and consistent with conventional pharmaceutical

practices. For example, for oral administration in the form of a tablet or capsule, the active ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, croscarmellose sodium and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture of active ingredient(s) and inert carrier materials. Suitable binders may include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, and corn sweeteners, natural and synthetic gums, such as acacia, tragacanth or sodium alginate, carboxymethyl cellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium sterate, sodium benzoate, sodium acetate, sodium chloride and the like. A particularly preferred tablet formulation of alendronate is that described in U.S. Patent 5,358,941, which is hereby incorporated by reference.

The compounds used in the instant method may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran co-polymer, polyhydroxylpropyl-methacrylamide and the like.

Patients suffering from rheumatoid arthritis may be male or female of any age. Women may be pre-or post-menopausal.

The following non-limiting examples are presented to better illustrate the invention.

EXAMPLE 1

Alendronate for the treatment and prevention of bone loss in patients with rheumatoid arthritis

220 men and women with active rheumatoid arthritis (as defined by the 1987 ARA Diagnostic Criteria), ages 18-80 are studied in a randomized double-blind clinical trial. Patients are randomized into 5 groups which receive either placebo, 2.5, 5, 10, or 20 mg/day alendronate orally each day for one year. In addition to standard RA therapy, patients are also given 1000 mg calcium and 250 IU Vitamin D daily.

After one year, the bone mineral density (BMD) of the spine, hip and total body are measured. In addition, the hand erosion score is assessed using standard techniques.

It is found that patients who receive daily oral alendronate at doses of 5-20 mg/day increase spine and hip BMD relative to both their baseline scores and to patients receiving placebo. The increase is statistically significant. Also, in patients receiving alendronate, hand erosion scores are decreased relative to baseline and placebo.

WHAT IS CLAIMED IS:

1. A method of preventing or treating generalized and/or periarticular bone loss associated with rheumatoid arthritis (RA) comprising administering an effective amount of a bisphosphonate selected from the group consisting of: alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid), etidronate (1-hydroxy-ethidene-bisphosphonic acid), pamidronate (3-amino-1-hydroxy-propyildiene-1,1-diphosphanate), risedronate (2-(3-pyridinyl)-1-hydroxyethylidene-bisphosphonic acid), clodronate (dichloromethylene-bisphosphonic acid), tiludronate (chloro-4-phenylthio-methylidene-bisphosphonic acid), ibandronic acid (1-hydroxy-3(methylpenty-lamino)-propylidene-bisphosphonic acid, and pharmaceutically acceptible salts of any of the foregoing, and mixtures of any of the acids and any of the salts to a patient suffering from RA.

2. A method according to Claim 1 wherein the bisphosphonate is alendronate.

3. A method according to Claim 2 wherein the alendronate is in the form of monosodium salt trihydrate.

4. A method according to Claim 3 wherein the alendronate is administered orally.

5. A method according to Claim 3 wherein the alendronate is administered in a dose of from 2.5 to 50 mg per day.

6. A method according to Claim 5 wherein the alendronate is administered in a dose of 5 mg, 10 mg, or 20 mg per day.

7. A method of treating bone loss associated with rheumatoid arthritis (RA) comprising administering a therapeutically effective amount of alendronate or a pharmaceutically acceptable salt thereof to a patient suffering from RA.

8. A method according to Claim 7 wherein the alendronate is in the form of monosodium salt trihydrate.

9. A method according to Claim 8 wherein the alendronate is administered orally.

10. A method according to Claim 8 wherein the alendronate is administered in a dose of from 2.5 to 50 mg per day.

11. A method according to Claim 10 wherein the alendronate is administered in a dose of 5 mg, 10 mg, or 20 mg per day.

12. A method of preventing bone loss associated with rheumatoid arthritis (RA) comprising administering a therapeutically effective amount of alendronate or a pharmaceutically acceptable salt thereof to a patient suffering from RA.

13. A method according to Claim 12 wherein the alendronate is in the form of monosodium salt trihydrate.

14. A method according to Claim 13 wherein the alendronate is administered orally.

15. A method according to Claim 13 wherein the alendronate is administered in a dose of from 2.5 to 50 mg per day.

16. A method according to Claim 15 wherein the alendronate is administered in a dose of 5 mg, 10 mg, or 20 mg per day.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/08361

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/66, 31/685
US CL :514/108

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/108

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,462,932 A (BRENNER ET AL) 31 October 1995, see claim 21.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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